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The dopamine theory of addiction: 40 years of highs and lows

David J. Nutt, Anne Lingford-Hughes, David Erritzoe and Paul R.A. Stokes

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Abstract

Addiction has for several decades come to be viewed as a disorder of the dopamine neurotransmitter system; however, this view has not led to new treatments. We review the origins of the dopamine theory of addiction and discuss the ability of addictive drugs to elicit the release dopamine in the human striatum. There is robust evidence that stimulants increase striatal dopamine release, some evidence for alcohol, but little if any for cannabis and opiates. Moreover, there is good evidence that striatal dopamine receptor availability and dopamine release are diminished in individuals with stimulant or alcohol dependence but not in individuals with opiate, nicotine or cannabis dependence. These observations have implications for understanding reward and treatment responses in various addictions.

Addiction is one of the great health problems facing the world today. Deaths from addictive substances, including tobacco and alcohol, amount to many millions of people per year¹, and currently available treatments for addiction have limited efficacy and application. Thus, there is a great need to better understand the brain mechanisms that are involved in addiction so that new, better-targeted interventions can be developed.

Brain research made a major breakthrough in the 1970s when the potential role of dopamine in addiction was discovered. This breakthrough stemmed from the finding of Olds and Milner² that rats would willingly and repeatedly self-stimulate particular areas in the brain with electricity, a process they called positive reinforcement. These areas were subsequently shown to comprise, in part, a set of dopamine neurons³, which explained why drugs that enhanced the actions of this neurotransmitter (for example, stimulants) increased electrical self-stimulation⁴. A subsequent series of largely US studies revealed that blocking dopamine receptors with neuroleptic drugs impaired the reinforcing effects of stimulants in rats and primates. This research clearly placed dopamine as the central neurotransmitter in stimulant addiction⁵ and suggested it had roles in reward, motivation and incentive behaviour⁶.

The next conceptual breakthrough came when a group of researchers in Sardinia, who pioneered the technique of brain microdialysis in rats, discovered that a range of other drugs of abuse (that is, not just stimulants) increased dopamine release in the nucleus accumbens, which is located in the ventral striatum⁷. This led to a general theory of addiction, which was that addictive drugs released dopamine but psychoactive drugs, that were not addictive, did not. The field developed rapidly from this point, with multiple replications of the early animal findings of dopamine being released by “addictive” drugs and reported confirmations in humans using neurochemical imaging. These findings led to immense investment in research to alter dopamine neurotransmitter function as a route to treat addiction. Disappointingly, despite four decades of intense research effort, this theory has not led to new treatments. In this Opinion article, we chart the history of the dopamine theory of addiction, explore the current evidence for this theory and suggest that initial optimism must now be cautioned with a more objective view of the role of dopamine in addiction.

Dopamine and the drug ‘high’

Studying *in vivo* dopamine function in humans became possible in the mid 1990’s with the development of radiotracer imaging techniques, such as ¹¹C-raclopride positron emission tomography (PET) and ¹²³I-IBZM single-photon emission tomography (SPECT). These tracers can be used to measure the availability of striatal dopamine D2/3 receptors and changes in striatal dopamine levels in the synapse (BOX 1)⁸.

The critical breakthrough in imaging the human dopamine system in addiction came

in 1994 when it was demonstrated that the combination of intravenous infusion of a central stimulant drug and SPECT or PET neurochemical imaging of dopamine D2/3 receptors could be used to indirectly measure dopamine release in the human striatum (BOX 1)^{9, 10}. The magnitude of this increase was later shown to predict the euphoria¹⁰ or 'high'¹¹ produced by the drug. This was interpreted as proving that the experience of pleasure (the rewarding action) of stimulant drugs in humans was mediated by striatal dopamine release, just as in rats⁷. This was a powerful message that many researchers sought to develop. A succession of other human studies followed, which showed that alcohol^{12, 13}, tobacco¹⁴, ketamine¹⁵ and cannabis¹⁶ increase striatal dopamine release in healthy participants and in non-dependent drug users, thereby providing support for the dopamine theory of addiction (FIG. 1).

Quite rapidly, the dopamine theory of addiction became generally accepted by the field, so that drugs which induced dopamine release were considered to pose a risk of abuse. An example of such a drug is modafinil, which is used to treat narcolepsy. A ¹¹C-raclopride dopamine imaging study found that modafinil produced an increase in dopamine release¹⁷. This finding was interpreted to mean that modafinil carries a potential risk for abuse, despite the increase in dopamine release not being associated with an increase in 'liking' scores¹⁷, and prior clinical evidence showing that modafinil was not reinforcing¹⁸. The dopamine theory of reward had a profound effect on the development of drugs that target the brain. Pharmaceutical companies routinely used rodent microdialysis assays of ventral striatal dopamine release to estimate the presumed abuse potential of new drugs, discarding compounds such as potential novel antidepressants if they elevated dopamine (D. J. N., unpublished observation). This is particularly concerning given the latest work using optogenetics to control dopamine neurons in mice shows that dopamine activity in ventral striatum is vital in resilience against depression¹⁹.

However, studies of alcohol²⁰, cannabis^{21, 22} and ketamine^{23, 24} showed that these abused drugs do not inevitably induce dopamine release in humans. Moreover, unlike with stimulants, an association between striatal dopamine release and pleasurable or hedonic effects of these substances was less apparent. For instance, there was no relationship between increased striatal dopamine release and any behavioural, subjective or physiological effects of cannabis^{16, 21}. In the case of alcohol, impulsivity and intoxication, but not 'high', were associated with increased dopamine levels^{12, 20}.

Despite these inconsistencies and the fact that all these drugs produced less dopamine release than intravenous administration of methylphenidate, a prevailing view developed that the dopamine system had a central role in addiction that was applicable to all addictive drugs. Dopamine became characterized as the 'pleasure' neurotransmitter in human brain; that is, the one that produces reward.²⁵⁻²⁷ This model of addiction even made

the cover of Time magazine <http://content.time.com/time/covers/0,16641,19970505,00.html>] and is widely quoted as a fact in current text books and by Wikipedia (for example, see the Wikipedia entries for “Reward system” and “Dopamine”).

From the beginning there were doubts about whether this theory applied to drugs other than stimulants and even whether dopamine release was central to the rewarding effects of stimulants in humans²⁸. Studies in rats showed that dopamine receptor blockade did not dampen the rewarding actions of opiates (for example, see²⁹), and subsequent clinical trials revealed that blocking dopamine receptors was generally ineffective in blocking the rewarding effects of stimulants in humans²⁸ or in treating human addiction (even stimulant addiction)³⁰. Moreover, several studies found that opiate administration was not associated with striatal dopamine release in opiate dependence. For example, a study in individuals addicted to heroin revealed that an intravenous dose of 50mg heroin had no effect on striatal dopamine levels despite producing a very pronounced euphoric ‘high’³¹. This finding was subsequently replicated in a study that further showed that expectation of a heroin reward (in the absence of actual heroin administration) also was not associated with dopamine release³².

Various studies of nicotine mostly suggest that this drug causes a small increase in ventral striatal dopamine levels. For example, smoking cigarettes has been shown to produce a 7% reduction in ¹¹C-raclopride PET binding (when compared with smoking de-nicotinised cigarettes)³³, whereas amphetamine produces a 10–20% reduction in the binding of this ligand³⁴⁻⁴² (FIG. 1). However, another study (in a small cohort) found that intranasal nicotine administration had no effect on ventral striatal dopamine release⁴³. This finding may be consistent with the idea that some of the effects of tobacco are due, in part, to the burning of tobacco-producing substances that block monoamine oxidase B — the enzyme that degrades dopamine⁴⁴.

Studies of ^Δ⁹-tetrahydrocannabinol (THC), the main psychoactive constituent of cannabis, found that this compound had even smaller effects on striatal dopamine release than nicotine. Administration of oral THC was associated with a non-significant reduction of around 2.5% in ventral striatal ¹¹C-raclopride binding²¹, inhaled THC was linked with a significant reduction of around 3.5% in ventral striatal ¹¹C-raclopride binding¹⁶, and intravenous THC was associated no significant change in ¹²³I-IBZM SPET binding²². The changes in ¹¹C-raclopride reported here for THC were all less than the test–retest variability of the tracer⁴⁵, which means that it is possible that they are the result of normal variation in the PET signal rather than being produced by THC administration. Although THC administration produced marked behavioural effects in all of these studies, such as perceptual distortions, cognitive disorganisation²¹ and even psychotic symptoms²², it seems that these cannot be satisfactorily explained by striatal dopamine release.

Lower dopamine function?

If the dopamine system is critically and universally involved in dependence to all drugs, we might expect changes in dopamine function to be apparent across all addictions. Two markers of abnormal dopamine function in drug dependence have emerged: the lower availability of striatal dopamine receptors and the diminished release of striatal dopamine in response to a pharmacological challenge (so-called blunting).

Lower striatal dopamine receptor availability. Early radio-tracer imaging studies revealed that cocaine users had lower striatal dopamine D2/3 receptor availability than matched controls⁴⁶. This was attributed to the effects of cocaine: cocaine induces dopamine release, which could be expected to downregulate post-synaptic dopamine receptors, leading to reduced receptor availability. This result has since been replicated in further cohorts of cocaine^{36, 47-51} and methamphetamine users⁵²⁻⁵⁴. Moreover, at least in cocaine addiction, this reduction in receptor radiotracer binding has been shown to result from the decreased expression of postsynaptic dopamine D2/3 receptors, rather than to higher synaptic dopamine concentrations that would compete with the radio-tracer⁴⁹ or to altered receptor affinity for dopamine⁵⁰. Decreased dopamine receptor availability has also been reported in individuals who are alcohol-dependent⁵⁵⁻⁶⁰ and, interestingly, higher striatal dopamine receptor availability may be protective against alcohol dependence in high-risk individuals (relatives of individuals with alcohol dependence)⁶¹.

However, differences in striatal dopamine receptor availability have not been as convincingly demonstrated in other addictions. Three studies have reported that individuals with opiate addiction have lower striatal dopamine receptor availability than healthy participants⁶²⁻⁶⁴, whereas we have found no change in receptor availability with opiate addiction³¹. In nicotine addiction, two related studies have reported lower striatal dopamine receptor availability in male but not female cigarette smokers^{65, 66} and three studies have found no differences in receptor availability between individuals who smoke and healthy non-smokers irrespective of gender⁶⁷⁻⁶⁹. There is no evidence of changes in striatal dopamine receptor availability in cannabis addiction⁷⁰⁻⁷⁴, and we could not find any published studies on such changes in ecstasy or ketamine users.

The observation of lower striatal dopamine D2/3 receptor availability in drug dependence also presents something of a paradox. One might predict that if striatal dopamine release was pleasurable, then lower receptor availability would lead to a reduction in this effect. However, a seminal study by Volkow and colleagues found the opposite; namely, individuals with low striatal dopamine D2/3 receptor levels (as measured by ¹¹C-raclopride PET) reported more pleasurable effects from stimulants^{75, 76}. Animal studies have also supported this finding. For example, in rats, low dopamine D2/3 receptor

levels in the striatum predict more cocaine ⁷⁷ but not heroin self-administration ⁷⁸, and in monkeys, higher striatal D2/3 receptor levels are associated with less cocaine intake⁷⁹. In addition, increasing dopamine receptors (through viral vector-mediated expression of the receptors) in the ventral striatum of dependent rats reduces both cocaine ⁸⁰ and alcohol intake ⁸¹.

These findings present a real challenge to the original theory that dopamine release is responsible for the euphoric effect of abused substances. If dopamine acting through D2/3 receptors is necessary to experience a drug 'high', then lower receptor availability should result in less, rather than more, rewarding drug effects.

Blunted dopamine release in dependence. In many, but not all addictions, individuals show a blunting of striatal dopamine release (that is, the release of striatal dopamine is decreased in these individuals compared with healthy individuals) after a pharmacological challenge with either the misused drug or a stimulant. This phenomenon was first reported in 1997, in cocaine-dependent participants after a methylphenidate challenge ⁸² and has been replicated several times in stimulant-dependent participants^{36, 51}. Decreased dopamine release has also been demonstrated in opiate dependence after a methylphenidate challenge ⁶⁴ and in alcohol dependence after an amphetamine challenge ^{57, 60} (FIG. 2). By contrast, no marked blunting of dopamine release was found in cannabis dependence after an amphetamine challenge ⁷².

Recent studies show that the extent of blunted striatal dopamine release in stimulant addiction may predict treatment response and vulnerability to addiction. In cocaine users, low stimulant-induced dopamine release was associated with a preference for cocaine to money ³⁶ and worse treatment outcomes ⁵¹. An elegant study of young people at ultra-high familial risk of addiction who used stimulants occasionally but were not yet dependent showed that amphetamine-induced dopamine release in these individuals was reduced compared with that in well-matched controls ⁸³. One interpretation of these data is that low dopamine release is a vulnerability to addiction, thus turning the dopamine theory on its head; instead of being the cause of addiction, dopamine might, if anything, have a role in resilience against becoming dependent and may be crucial for recovery from addiction ⁵¹. However, it is also possible that ultra-high risk participants had not become addicted because they experienced less dopamine release.

Addiction to the dopamine theory?

It is worth reflecting on why enthusiasm for the universal dopamine theory of addiction developed and then came to dominate the addiction field. There are several interacting factors. First, the animal dialysis studies were so novel and compelling and were seemingly confirmed by the beautiful studies of Schultz, which showed that dopamine neurons fired in response to rewards in monkeys⁸⁴. However, the relative discrepancies in the magnitude of dopamine release elicited by different drugs⁷ should have given the field pause for thought. The stimulants produced striatal dopamine elevations that were many-fold greater than those produced by the other drugs, yet human experience suggests that stimulants are not more pleasurable or addictive⁸⁵. Findings from studies investigating only stimulants (generally cocaine or amphetamine) were often discussed as though they applied to all addictions, even though there was no evidence for such an assumption⁸⁶. Indeed, where studies have been conducted using the same animal models, it is clear that stimulants differ from opioids, for example in terms of the effects of low dopamine receptor number and drug self-administration^{77, 78}.

Second, the methylphenidate experiment in humans showed such a clear relationship between dopamine release and the perceived 'high' that it appeared mechanistic — the more dopamine release the bigger the 'high'⁷⁵. However, what was overlooked was the fact that methylphenidate and other stimulants act specifically on the dopamine system to increase dopamine levels. Thus, dopamine must be the proximal mediator of any psychological response to stimulants, and it should not be surprising that the change in striatal dopamine release correlates with the subjective 'high'. However, this is an association rather than proof that the change in striatal dopamine levels mediates the 'high' for stimulants. For other psychoactive drugs that only indirectly act on dopamine neurons — such as alcohol and nicotine that act via modulating dopaminergic neuronal firing in the ventral tegmental area — the association between changes in dopamine levels and 'high' has been harder to show.

Increased dopamine release has also been reported in rewarding activities such as playing computer games⁸⁷, the placebo response to L-dopa⁸⁸, in meditation⁸⁹ and eating behaviours⁹⁰. These findings have been used to 'prove' the dopamine theory of addiction, as they associate rewarding activities with dopamine release and so generalize the model to one that says all rewarding activities must be mediated by dopamine release. However, these studies imaged small numbers of participants and are often not replicated. The apparent rush to publish that any given pleasure-inducing drug or behaviour can induce dopamine release reflects one of the more worrying and pervasive aspects of science today — the pre-eminence given to reporting 'positive' data in support of currently influential theories. There is a concern that the classic Popperian approach to science, namely refuting

hypotheses, may be lost in the desire to publish papers that ‘prove’ the theory and which are then well cited but are often not replicated.

Does dopamine have other roles?

Dopamine has many roles in normal brain function. In the cortex, dopamine is important for executive functions such as attention and working memory⁹¹; in the basal ganglia it is necessary for motivational salience, reward and fluent motor function; and in the hypothalamus it regulates prolactin release. Dopamine also has been shown to have a major role in the pathogenesis of a proportion of cases of psychosis⁹² and to be involved in positive mood in humans⁹³.

Changes in dopamine function in the basal ganglia can lead to compulsive-type behaviours. One theory of dopamine’s involvement in stimulant addiction is that the initial pleasurable effects of these drugs are detected in the nucleus accumbens, and that with repetitive use of the drugs, the drug taking behaviour becomes encoded as habit in the caudate and putamen, through progressive activation of the spiral of interacting striatal-cortical circuits^{94, 95}.

As in rats, dopamine receptor availability in humans might relate to impulsivity (which itself is a risk factor for addiction)^{96, 97}. It has been proposed that low D2/3 receptor availability and low dopamine release in the striatum — as described in substance addiction, obesity and attention deficit hyperactivity disorder (ADHD) — are neurobiological markers of increased impulsivity⁹⁶. The relationship between impulsivity and dopaminergic function has been investigated in another disorder with high levels of impulsivity, pathological gamblers (that is, individuals addicted to gambling). This disorder, was recently re-categorized from an ‘impulse control disorder’ in DMS-IV to a ‘behavioural addiction’ in DSM-5 due to clinical and cognitive similarities with substance addiction. Thus pathological or disordered gambling serves as a useful model to study addiction in the absence of any drug-induced changes in neurotransmitter function⁹⁸.

In contrast to substance addiction, no differences in baseline D2/3 receptor availability have been found in pathological gamblers compared with healthy controls^{99, 100}. However, in one of these studies, striatal D2/3 receptor availability was inversely correlated with mood-related or ‘rash’ impulsiveness¹⁰⁰ and in the other, D2/3 receptor availability positively correlated with impulsiveness in the substantia nigra, a dopamine D3 receptor-rich brain region⁹⁹. Unlike the blunted stimulant-related dopamine release that is seen in substance addiction, dopamine release was increased in the dorsal striatum after amphetamine administration in pathological gamblers compared with healthy volunteers¹⁰¹. This increase in dorsal striatal dopamine was predicted by the availability of D3 receptors, and the authors of this study proposed that D3-related mechanisms might contribute to

sensitization in this behavioural addiction¹⁰¹. The finding of increased stimulant-related dopamine release in pathological gamblers would also be consistent with the development of pathological gambling that is associated with dopamine replacement therapy in Parkinson's disease. Indeed, patients with Parkinson's disease with impulsive-compulsive behaviours, such as pathological gambling, show increased ventral striatal dopamine release after the presentation of rewarding cues¹⁰² in a similar way to cocaine users who show increased dorsal striatal dopamine release after the presentation of cocaine related cues¹⁰³.

Therefore, depending on the disorder associated with impulsivity, either lower or higher dopaminergic function has been found. It may be that rather than a linear relationship, an inverted-U type of response function for dopamine underpins the relationship with impulsivity such that an increase or decrease in dopamine may be required to improve inhibitory control; for example, an increase in dopamine may improve inhibitory control in ADHD but a decrease in dopamine may improve such control in gambling associated with dopamine replacement in Parkinson disease.

Dopamine may also have a role in regulating the motivation to seek drugs. The induction of craving is associated with cue-induced striatal dopamine release in cocaine users¹⁰³⁻¹⁰⁵, although this is not the case in heroin addicts³². Dopamine has been proposed to have a role in motivation more generally⁹⁴, which could explain why in stimulant users, it might both drive use and be necessary for recovery from addiction. Dopamine also has a role in executive function¹⁰⁶ (which includes inhibitory control) and, by acting through a top-down cortico-striatal mechanism, may have a role in preventing addiction and other dyscontrol disorders such as overeating¹⁰⁷.

There is further evidence to support a possible protective role for dopamine in some drug users. A study in non-treatment seeking stimulant-dependent individuals¹⁰⁸ showed that the dopamine D2/3 receptor agonist pramipexole had different effects on psychological performance in a Stroop task and related functional MRI measures in individuals with high drug-related compulsivity versus individuals with low drug-related compulsivity. If this finding is replicated with cocaine and in people with other drug dependencies, it might lead to a more sophisticated view of dopamine in addiction and, potentially, to targeted interventions such as dopamine-promoting agents in people with addiction who exhibit impulsivity. Moreover, these results found using pramipexole¹⁰⁸ may explain the partial efficacy of dopamine receptor agonists such as bromocriptine¹⁰⁹, and dopamine metabolism inhibitors such as disulfiram³⁰ in the treatment of alcohol and cocaine dependence, respectively.

Other aspects of dopamine functioning in addiction such as the role of extra-striatal dopamine and the influence of drug cues on dopamine responses and future research needs are outlined in BOX 2.

Limitations

Neurochemical imaging has provided crucial advances in our understanding of the role of the human dopamine system in addiction; however, there are limitations associated with the imaging technique and with the populations that have been imaged.

Current dopamine radiotracers bind to D2/3 receptors irrespective of their synaptic location and most, with the exception of [^{11}C]-(+)-4-propyl-3,4,4a,5,6,10b-hexahydro-2*H*-naphtho[1,2-*b*][1,4]oxazin-9-ol (^{11}C -PHNO) which preferentially binds to D3 receptors, bind to both dopamine D2 and D3 receptors. This means that for most studies it is difficult to assess whether differences in dopamine radiotracer binding between populations reflect altered D2 or D3 receptor availability. It also means that it is not possible to determine whether differences in binding reflect alterations in pre- or postsynaptic D2/3 receptors, although as animal studies show that the majority of striatal dopamine D2/3 receptors are localised postsynaptically¹¹⁰, most groups have interpreted differences as changes in postsynaptic D2/3 receptors. The sensitivity of neurochemical imaging to lower levels of dopamine release produced by pharmacological challenges is also limited by the variability in the PET or SPECT imaging signal, so that changes of 5% or less in binding could be a result of lower levels of dopamine release or variability in the signal. This is an important limitation as a primate study has shown that, at least for the SPECT radiotracer ^{123}I -IBZM, which has a lower resolution than PET radiotracers such as ^{11}C -raclopride, a 1% decrease in binding equates to a 40% increase in dopamine release¹¹¹.

There are also limitations in the types of populations imaged; the large majority of studies have imaged dependent populations and only a few (for example, see REF.⁸³) have imaged those at high risk of developing addictions. This means that we do not know whether the changes in dopamine function reported in dependence are a consequence of substance use or are present before the onset of addiction and may mediate vulnerability.

The fact that there are only few dopamine neurochemical imaging studies available for the majority of the investigated substances, combined with the problem of different methods employed to define striatal regions (the latter partly due to the gradual improvement of scanning techniques over the past few decades), means that conducting meta-analyses in order to synthesize findings across each addiction has so far proven to be challenging.

Conclusions

The dopamine theory of reward and addiction, which states that dopamine release mediates reward and so leads to addiction, has had huge traction. However, it became accepted as a ‘universal’ theory without properly accounting for findings from studies in different drug addictions that did not support the theory. Tellingly, the dopamine theory has not led to any new treatments for addiction. We suggest that the role of dopamine in addiction is more complicated than the role proposed in the dopamine theory of reward. We propose that dopamine has a central role in addiction to stimulant drugs, which act directly via the dopamine system, but that it has a less important role, if any, in mediating addiction to other drugs, particularly opiates and cannabis.

Addiction is a complex mixture of behaviours and attitudes that vary from drug to drug and from user to user, and it is unlikely that a single neurotransmitter could explain every aspect of addiction. We foresee that addiction will be conceptualised as a multiple neurotransmitter disorder in which the dopamine system is central to stimulant addiction but in which other neurotransmitter systems, such as the endogenous opiate or GABA systems, have important roles in other drug addictions. For example, endogenous opiates have been shown to be released by stimulants ¹¹² and alcohol ¹¹³; higher opiate receptor availability has been found in cocaine ^{114, 115}, opiate ¹¹⁶ and alcohol dependency ¹¹⁷⁻¹¹⁹; and alcohol dependence and pathological gambling can, to some extent, be treated with opioid antagonists such as nalmefene ¹²⁰⁻¹²². Moreover, individuals with alcohol dependence have lower limbic GABA_A receptor availability ¹²³, whereas participants with a history of cigarette smoking have higher limbic GABA_A receptor availability ¹²⁴.

In conclusion, this account of the rise and fall of the universal dopamine theory of addiction serves as a lesson in neuroscience research. Unifying theories, though intrinsically appealing, should be subject to careful scrutiny just like other theories — and perhaps even more so, as they can lead the field into directions that ultimately prove to be unfruitful.

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Competing interests

The authors declare competing interests: see Web version for details.

FURTHER INFORMATION

Cover of Time magazine: <http://content.time.com/time/covers/0,16641,19970505,00.html>

Wikipedia: <http://en.wikipedia.org>

Box 1 | Imaging dopamine receptors and dopamine release

Imaging dopamine in the human striatum.

Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are quantitative radioactive imaging techniques that can be used to measure the availability of receptors and transporters, as well as the release of neurotransmitters. In the case of the dopamine system, radiotracers such as ^{11}C -raclopride (for PET) and [^{123}I]-iodobenzamide (for SPECT) can reliably measure the availability of dopamine D2/3 receptors in the human striatum, the brain area with the highest density of these receptors. This includes the ventral striatum (also known as the nucleus accumbens), the region of the striatum that seems particularly involved in the acquisition of drug addiction. Most D2/3 radiotracers, and in particular the ones with agonist properties such as [^{11}C]-(+)-4-propyl-3,4,4a,5,6,10b-hexahydro-2*H*-naphtho[1,2-*b*][1,4]oxazin-9-ol (^{11}C -PHNO), also have the ability to compete with the brain's endogenous dopamine to bind to D2/3 receptors¹²⁵. Increases in extracellular dopamine levels elicited by pharmacological challenges, such as with methylphenidate¹²⁶ or amphetamine¹⁰, or non-pharmacological manipulations, such as stress, playing a video game or cue-induced drug craving⁸, can be detected as a decrease in the radiotracer binding due to increased competition for the striatal D2/3 receptor (for a review, see REF⁸).

Extrastriatal dopamine imaging

The development of higher affinity radiotracers for D2/3 receptors such as ^{18}F -fallypride, ((S)-N-((1-ethyl-2-pyrrolidinyl)methyl)-5-bromo-2,3-dimethoxybenzamide) (^{18}F -FLB 457)¹²⁷ and [^{11}C]-PHNO¹²⁸ has made it possible to image these receptors in brain regions outside the striatum (for example, in the frontal cortex), where the density of D2/3 receptors is lower. Radiotracers such as ^{11}C -propyl-norapomorphine and in particular ^{11}C -PHNO not only have high-affinity agonist properties but also have a higher affinity for dopamine D3 receptors over D2 receptors. This additional quality enables quantification of D3 availability and release in key areas of the brain in addiction such as the globus pallidum, ventral tegmental area, amygdala and hypothalamus¹²⁹.

Box 2 | Key Issues and perspectives for future research

To optimise our understanding about the relationship between the human dopamine system and addictive drugs, future research should consider a number of questions. First, who is being imaged? In selecting research participants, it is crucial to carefully describe factors that likely influence dopamine function, such as the lifetime use of alcohol and drugs, prior or current treatments, and periods of and current length of abstinence. Most individuals with a drug addiction use more than one substance and, other than tobacco smoking, such comorbidity is usually an exclusion criterion for studies in addiction. Selection of a control group that matches potentially important confounders — such as intelligence quotient or years of education, family history and alcohol, tobacco and other drug use — can be challenging.

Second, how is dopamine release induced? Stimulants are traditionally used in studies to increase dopamine levels. However, this pharmacological challenge may not be salient to individuals with addiction. For instance, many individuals with alcohol use disorders do not find stimulants rewarding, so in these individuals, any changes in dopamine levels that are induced by stimulants reflect what is available for release but does not inform us about ‘dopamine and reward’. Indeed, in such individuals, stimulant administration may be experienced as aversive. In some studies, addicted individuals were administered their ‘drug-of-choice’, but not in the way they would normally self-administer it (for example, nicotine inhalators versus smoking), thereby reducing the salience of the drug, which could affect dopamine responses. An inherent limitation of PET protocols is that the drug-taking context cannot be simulated, but at least pharmacological and behavioural challenges should be optimised to reflect ‘usual’ drug behaviour.

Third, what is the role of cortical dopamine function? Most neurochemistry studies in addiction have imaged dopamine function in the human striatum. Such studies do not capture the importance of dopamine in mediating processes that are key to addiction, such as compulsion and executive function, which are largely cortical. We suggest that an important step for future studies is to focus on cortical dopamine function in addictions, particularly as great advances in human cortical dopamine imaging have been made over the past decade.

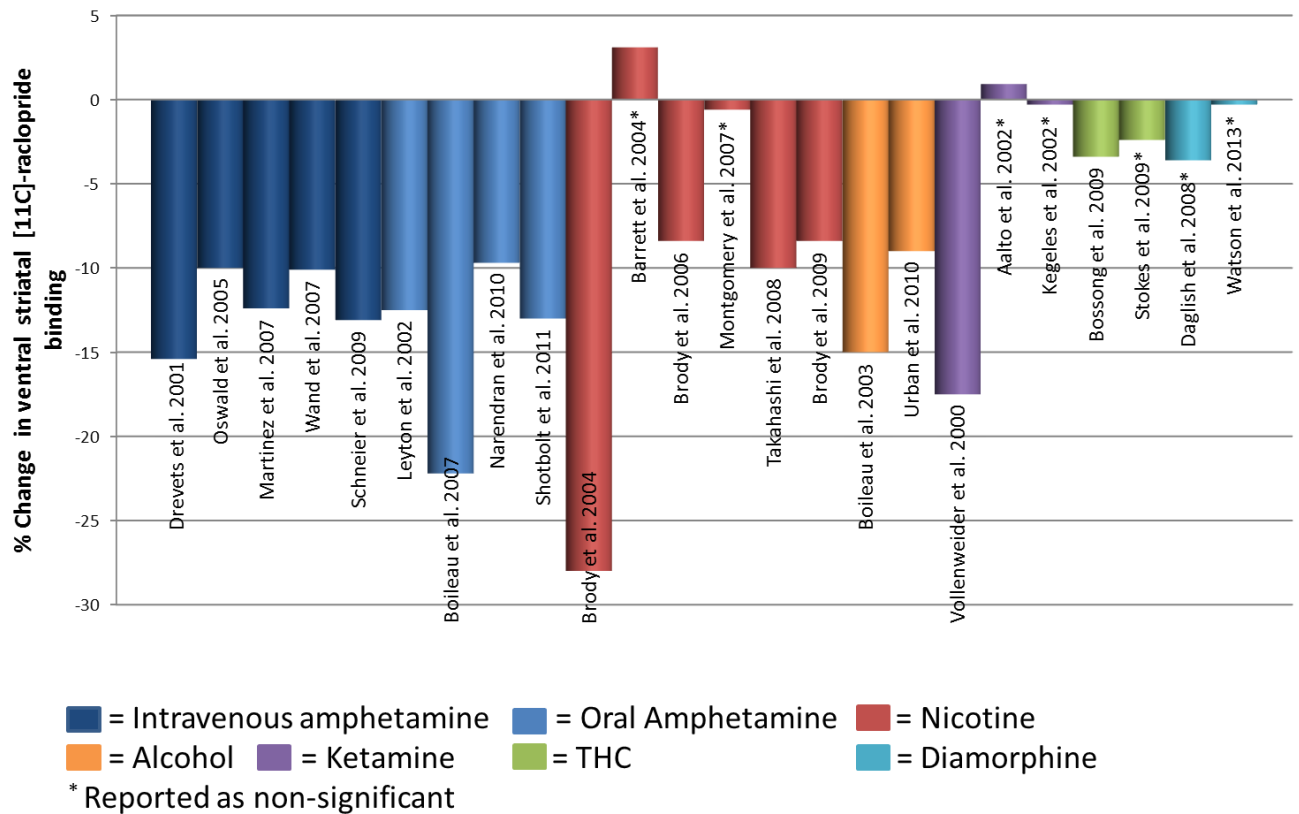


Figure 1 | The effect of abused substances on human ventral striatal dopamine

release The studies contained in the figure use the the dopamine D2/3 receptor PET radiotracer ^{11}C -raclopride to investigate the effect of abused substances on dopamine release in the ventral striatum. Decreases in ^{11}C -raclopride PET binding occurs as a consequence of increased competition between dopamine and the tracer and so percentage decreases in ^{11}C -raclopride binding reflect increased synaptic ventral striatal dopamine levels. These studies show consistent significant increases in ventral striatal dopamine levels produced by amphetamine and alcohol administration, less consistent increases produced by nicotine, and non-significant or small increases associated with diamorphine, THC or ketamine administration. The data presented here are derived from published studies describing changes in the ventral striatum, as this striatal area is the most relevant one to the theory of reward and dopamine; some studies are therefore not represented since data were available only for whole striatum. *Studies in which the change in ^{11}C -raclopride binding was reported as non-significant. THC, $^{\Delta 9}$ -tetrahydrocannabinol. Data from REFs^{12-16, 21, 23, 24, 31-43, 130-132}. The studies contained in the figure are broadly comparable although there is some variability in the number participants imaged between studies and statistical tests used (largely t-tests).

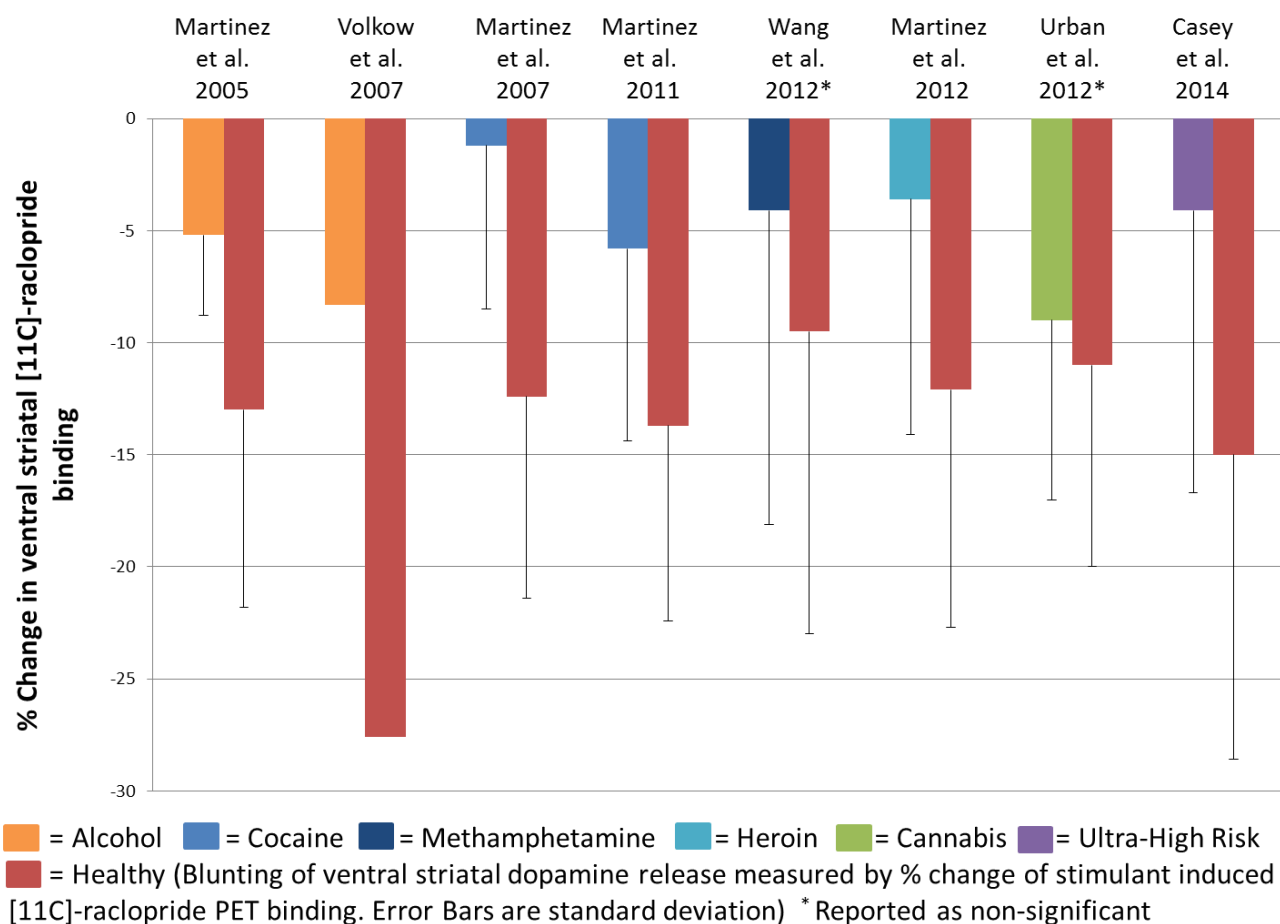


Figure 2 | Investigating diminished ventral striatal dopamine release in addictions.

These studies use the dopamine PET radiotracer ^{11}C -raclopride to investigate whether diminished ('blunted') ventral striatal dopamine release occurs after administration of a stimulant (amphetamine or methylphenidate) in a range of substance addictions. Decreases in ^{11}C -raclopride PET binding occurs as a consequence of increased competition between dopamine and the tracer and so percentage decreases in ^{11}C -raclopride binding reflect increased synaptic ventral striatal dopamine levels. The studies contained in the figure demonstrate significantly diminished ventral striatal dopamine release in alcohol, cocaine and heroin dependent individuals, and also in individuals at ultra-high risk to develop addiction, but no diminished release in cannabis or methamphetamine users. We selected studies which administered either amphetamine or methylphenidate as these directly target the dopamine system to ensure that any differences in dopamine levels would reflect changes in this system. For each study, the percentage change in ^{11}C -raclopride binding is given for healthy participants and for the addicted population whose substance of addiction is depicted by the bar colour. The error bars show standard deviation. *Denotes a significant difference (according to the original study) in ^{11}C -raclopride binding between the healthy participant and addiction groups. Data from REFs^{36, 51, 54, 57, 60, 64, 72, 83}. Volkow and colleagues⁶⁰ do not report standard deviation in change in ^{11}C -raclopride PET binding. The

studies contained in the figure are broadly comparable although there is some variability in the number participants imaged between studies and statistical tests used (largely t-tests).